35. A vector of Claim 29, wherein the oncogene or proto-oncogene product is a protein kinase.

REMARKS

Applicants affirm the provisional election with traverse to prosecute the invention of Group I, Claims 1-23 and 27-31.

Claim Amendments

Claims 1, 3-6, 8-9, 11-12, 15, 17-20, 22-23, and 29 have been amended to replace "tumor associated antigen" with ---oncogene or oncogene product--- or ---oncogene product---. This amendment is responsive to the Examiner's comments on page 6, paragraph 1.

Claims 1, 6, 8, 15, 20, 22-23, 27 and 30 have been amended to replace "a cell encoded" with ---of cellular origin--- in response to the Examiner's comments on page 9, paragraph 2.

Claims 4, 11 and 18 have been amended in response to the Examiner's comments on page 9, paragraph 2, to make clear that loss of oncogenic activity is due to a mutational alteration.

Claims 6-7, 12 and 20-21 have been amended in response to the Examiner's comments on page 6, paragraph 2.

Claims 5, 10, 19 and 30 have been amended, in response to the Examiner's comments on page 10, lines 1-5 to make clear that the recited portion is capable of stimulating an immune response.

Claims 2 and 16 have been amended to remove the reference to "species" in response to the Examiner's comments on page 9, paragraph 2.

Dependent Claims 16-21 have been amended by Applicants sua sponte to correct the subject matter classification to correspond with that of Claim 15 on which they depend.

Claim 27 has been amended, in response to the Examiner's comments on page 10, lines 8-15, and to clarify the structural relationships of the elements.

Applicants have added new Claims 32-35 which serve to define the invention with greater particularity. Specifically, these claims relate to oncogene or proto-oncogene products which having a protein kinase functionality. Support for these new claims is found in the specification on page 8, lines 19-22.

Rejection Under 35 U.S.C. 101:

Claims 15 and 22 have been rejected under 35 U.S.C. 101 as lacking patentable utility. The Examiner asserts that there is nothing in the specification from which it may be inferred that inoculating a tumor bearing individual with a recombinant pox virus capable of expressing a tumor associated antigen present on the tumor will immunize the individual against the particular oncogene product. In support of this rejection the Examiner asserts that "an individual afflicted with such a tumor would have already, if possible, mounted an immunological response against the antigen."

The Lathe et al. reference, which was cited by Applicants in the specification, and by the Examiner as the basis for a rejection under 35 U.S.C. 102(a), is relevant on this issue; in particular the discussion on page 880 regarding the inoculation of tumor bearing animals with recombinant vaccinia. In 50% of the animals so treated, tumor growth halted and regression proceeded to complete tumor elimination. In the control group of unvaccinated animals the tumors were not rejected. This demonstration by Lathe et al. represents a clear contradiction to the Examiner's statement set forth here in the preceding paragraph. The tumor bearing mice did not mount an effective immunological response until after recombinant vaccinia inoculation.

The argument set forth above should in no way be construed as an admission of obviousness by Applicants with respect to the subject invention in light of Lathe et al. A distinction of patentable significance between Applicants' disclosure and that of Lathe et al. relates to the source of the gene introduced by vaccinia. Lathe et al. introduced a viral gene product into a host cell and determined that an effective response was mounted by the host.

Applicants, on the other hand, disclose that a gene of cellular origin, when introduced into a host cell via a pox viral vector also stimulates an immune response. It was unobvious to one skilled in the art at the time that such a cellular gene could elicit such a response when introduced into a cell. Having shown that a cellular product can elicit such a response, it follows from Lathe et al. that such an immunogenic product can be used to elicit a

response in a host bearing a tumor prior to vaccination.

Rejection Under 35 U.S.C. 112:

Claims 1-23 and 27-31 have been rejected as non-enabled under 35 U.S.C. 112, first paragraph. In response to the §112 rejection found on pages 4-5 of the Office Action, a deposit satisfying the availability and maintainance requirements of MPEP 608.01 will be made. Additionally, as described above the claims have been amended extensively in response to the Examiner's objections.

The Examiner asserts in paragraph 2 of page 6 that the specification does not teach the immunization of any tumor bearing individual against a tumor-associated antigen nor does it teach how to identify what antigen is borne by the tumor with which the individual is afflicted. Applicants respectfully traverse this rejection. First, the specification does teach the immunization of a mouse against an oncogene product; in particular, the neu gene product. The specification further shows that such an immunization is effective in preventing tumor growth in the mouse. Although it is true that there is no example in the specification which demonstrates effective immune therapy in an individual bearing a tumor at the time of inoculation, the success of such therapy is predictable given the teaching of the prior art (this point is elaborated above within the context of the 35 U.S.C. 101 rejection). In response to the Examiner's comment regarding a means for identifying an oncogene product, such means are well known to those skilled

in the art. Monoclonal antibodies specific for particular oncogene products would be used to screen tumor biopsies. Such techniques are commonly employed in many diagnostic techniques.

The Examiner further states that "the specification does not teach recombinant vaccinia virus comprising the ros gene, the trk gene, the kit gene, the c-erb B gene, any oncogene (other than neu) or proto-oncogenes, or any growth factor receptors, or growth factor-like receptor molecules.

Although it is true that the Exemplification is limited to the neu oncogene, the neu gene, as well as the other specified oncogenes belong to a family of genes (oncogenes or proto-oncogenes) having similar properties. A recent report by Takahashi et al. (Mol. Cell. Biol. 7:1378-1385 (1987) which describes the ret gene also discusses the relationship between a number of these genes. "Analysis...of ret revealed 40 to 50% homology with other tyrosine kinases including ros, abl, src, fms, fps, human insulin receptor and human epidermal growth factor receptor. In addition, it showed similar homology with other recently identified tyrosine kinases including lst$^+$, met, neu, kit and trk." The conserved regions among these tyrosine kinases include a lysine thought to be involved in ATP binding and a putative phosphotyrosine accepter site.

Takahashi et al. also report that the ret gene encodes a putative membrane anchoring domain. "Similar transmembrane domains are found in the other tyrosine kinases which are known cell surface receptors, including the insulin and epidermal

growth factor receptors and fms, as well as in ros, trk and neu." In each case the putative trans-membrane domain is located 50 to 70 amino acids upstream of the start of the tyrosine kinase domain.

Yarden et al. (EMBO J. 6:3341-3351 (1987)) describe the relationship between a variety of growth factor receptors including epidermal growth factor, insulin, platelet-derived growth factor, insulin-like growth factor and macrophage colony stimulating factor. Several oncogenes are derived from the proto-oncogenes these receptors. Among the common features of these glycoproteins are an extracellular ligand binding domain, connected by a single membrane-spanning segment to an intracellular domain that possesses tyrosine-specific protein kinase activity.

Other references which discuss the relationship between members of the oncogene family include: Slaman et al., Science 235:177-182 (1987); Martin-Zanka et al., Nature 319:743-748 (1986); Besmer et al., Nature 320:415-421 (1986); and Coussens et al., Science 230:1132-1139 (1985). A copy of the Coussens et al. references is included herewith for the Examiner's convenience. Other references cited herein are references of record.

The structural similarities of these members of the oncogene family support the breadth of the claims as drawn. One of ordinary skill in the art would expect that each member of the oncogene family would generate anti-tumor immune response given Applicants' findings with respect to the neu gene product.

On page 8, paragraph 1, the Examiner asserts that the specification does not support claims to pox virus other than vaccinia. Applicants respectfully traverse this rejection. Those skilled in the art are familiar with the overall similarity in organization between the various members of the pox virus family. One skilled in the art could, without undue experimentation, identify a non-essential region in a pox virus, replace it with a gene encoding an oncogene or proto-oncogene, and infect a host.

On page 8, the Examiner asserts that Applicants' failure to teach a means to identify and clone any tumor associated antigen would necessarily result in undue experimentation on the part of one skilled in the art. Applicants traverse this rejection; the cloning of many such genes has been reported in the literature and such clones are available to scientists in the field. References reporting the cloning of c-kit (Yarden et al.), c-ros (Majarajan et al.), c-neu (Bargmann et al.), c-erb-B-2 (Yamamoto et al.) and c-trk (Martin-Zenka et al.) have been previously cited in the Information Disclosure Statement. Given the breadth of information in the public domain regarding the cloning of these oncogenes, as well as the availability of some as cloned sequences, any manipulation required to transfer and express the sequences in a pox virus vector would be strictly routine.

In response to the Examiner's comment on page 9, paragraph 2, Applicants have amended Claims 2 and 16 to remove the reference to "species". Applicants

believe that these claims are definite in their amended form.

Applicants respectfully traverse the rejection set forth on page 10, paragraph 2. Contrary to the Examiner's assertion, the genes enumerated in independent Claims 5, 10, 19 and 30 are genes of cellular (as opposed to viral) origin.

Rejections Under 35 U.S.C. 102 and 35 U.S.C. 103

Claims 1-23 and 27-31 have been rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Lathe et al. Lathe and co-workers expressed three polyoma virus proteins in separate vaccinia recombinants. The rats mounted an immune response which was effective in preventing tumor growth.

The work of Lathe and co-workers is clearly non-anticipatory with respect to Applicants' claimed invention. Lathe et al. expressed viral encoded proteins in an immunized animal whereas Applicants expressed proteins encoded by cellular genes. Applicants' claims have been amended to clearly incorporate this limitation as to the source of the gene.

This same distinction is highly relevant to the alternative rejection under 35 U.S.C. 103 as well. The viral encoded proteins of Lathe et al. would be predicted by one skilled in the art to be highly immunogenic in a cell. However the cellular gene product employed by Applicants is homologous to a protein indigenous to the cell. It was surprising, therefore, to find that an organism can mount an

immune response to a protein having such a high degree of homology with a cellular constituent.

Claims 1-23 and 27-31 have been rejected under 35 U.S.C. 103 as being unpatentable over Kornbluth or Mansour in view of Davis and Paoletti. The arguments set forth above apply with equal weight to these references. None of these references so much as hint at the expression of a cellular oncogene in vaccinia. Mansour et al. employed an adenovirus vector to express polyoma virus tumor antigens. Kornbleuth et al. discuss tumor induction by the middle T antigen of polyoma virus. None of the passages in the Davis text relates to cellular oncogenes of this invention and, in fact, most of the cited sections relate to viral oncogenes.

For the foregoing reasons, Applicants request that the Examiner reconsider and withdraw all rejections. If the Examiner believes that a telephone conversation will expedite prosecution of this application, the Examiner is urged to call Applicant's Attorney at 617-861-6240.

Respectfully submitted,

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